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Autoimmune liver disease, autoimmunity and liver transplantation

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Summary

Primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH) represent the three major autoimmune liver diseases (AILD). PBC, PSC, and AIH are all complex disorders in that they result from the effects of multiple genes in combination with as yet unidentified environmental factors. Recent genome-wide association studies have identified numerous risk loci for PBC and PSC that host genes involved in innate or acquired immune responses. These loci may provide a clue as to the immune-based pathogenesis of AILD. Moreover, many significant risk loci for PBC and PSC are also risk loci for other autoimmune disorders, such type I diabetes, multiple sclerosis and rheumatoid arthritis, suggesting a shared genetic basis and possibly similar molecular pathways for diverse autoimmune conditions. There is no curative treatment for all three disorders, and a significant number of patients eventually progress to end-stage liver disease requiring liver transplantation (LT). LT in this context has a favourable overall outcome with current patient and graft survival exceeding 80% at 5 years. Indications are as for other chronic liver disease although recent data suggest that while lethargy improves after transplantation, the effect is modest and variable so lethargy alone is not an indication. In contrast, pruritus rapidly responds. Cholangiocarcinoma, except under rigorous selection criteria, excludes LT because of the high risk of recurrence. All three conditions may recur after transplantation and are associated with a greater risk of both acute cellular and chronic ductopenic rejection. It is possible that a crosstalk between alloimmune and autoimmune response perpetuate each other. An immunological response toward self- or alloantigens is well recognised after LT in patients transplanted for non-autoimmune indications and sometimes termed "de novo autoimmune hepatitis". Whether this is part of the spectrum of rejection or an autoimmune process is not clear.

In this manuscript, we review novel findings about disease processes and mechanisms that lead to autoimmunity in the liver and their possible involvement in the immune response *vs.* the graft after LT.

Keywords: Autoimmunity; Primary biliary cirrhosis; Primary sclerosing cholangitis; Autoimmune hepatitis; Genome-wide association studies; Recurrence; Rejection; *De novo* autoimmune hepatitis.

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Introduction

Autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are the tree major forms of autoimmune liver disease, which differ according to the focus of autoimmune injury, the pattern of inflammation and the clinical phenotype.

In AIH, the autoimmune injury affects the hepatocytes, leading to the histological picture of interface hepatitis. In PBC, the autoimmune injury affects the small, interlobular bile ducts, causing the typical appearance of non-suppurative, destructive cholangitis. In PSC, autoimmune or immune-mediated injury affects the medium-sized intra- and extrahepatic bile ducts, causing concentric and obliterative fibrosis and multifocal bile duct stricturing.

AIH, PBC, and PSC represent complex disorders, in that they result from the interaction between genetic and environmental factors (Fig. 1). In recent years, there have been major efforts to delineate the genetic architecture of these conditions. Recent genome-wide association studies (GWAS) and iCHIP-association studies [1–8] identified numerous risk loci for PBC and PSC that host genes involved in innate or acquired immune responses. These findings have resulted in a better understanding of the pathogenic mechanisms underlying these immune-mediated conditions, highlighting common immune pathways between clinically associated disorders and explaining the tendency for patients and their families to suffer from multiple autoimmune conditions. This translates in the possibility of unique immunologic pathways for therapeutic intervention. The implication is that biological processes involved in loss of immune tolerance to one self-antigen (such as CYP2D6 in the case of some models of AIH or PDC-E2 in PBC) might be the same for other self-antigens (such as thyroid peroxidase in thyroid disease).

All three disorders have a progressive course that, if untreated, develop into liver failure requiring liver transplantation (LT). The aim of treatment is to abolish or reduce inflammation, cholestasis and progression of fibrosis. Standard therapy in AIH consists of a combination of corticosteroids and azathioprine, which is effective in 80% of patients; however progression may occur despite seemingly effective treatment. Other immunosuppressive agents such as mycophenolate mofetil, d-penicillamine, sirolimus and anti-T cell therapies have been tried in refractory cases with limited success [9]. The only licensed therapy for PBC and PSC is ursodeoxycholic acid (UDCA) [10]. In PBC, response to UDCA has a favourable effect on long-term survival

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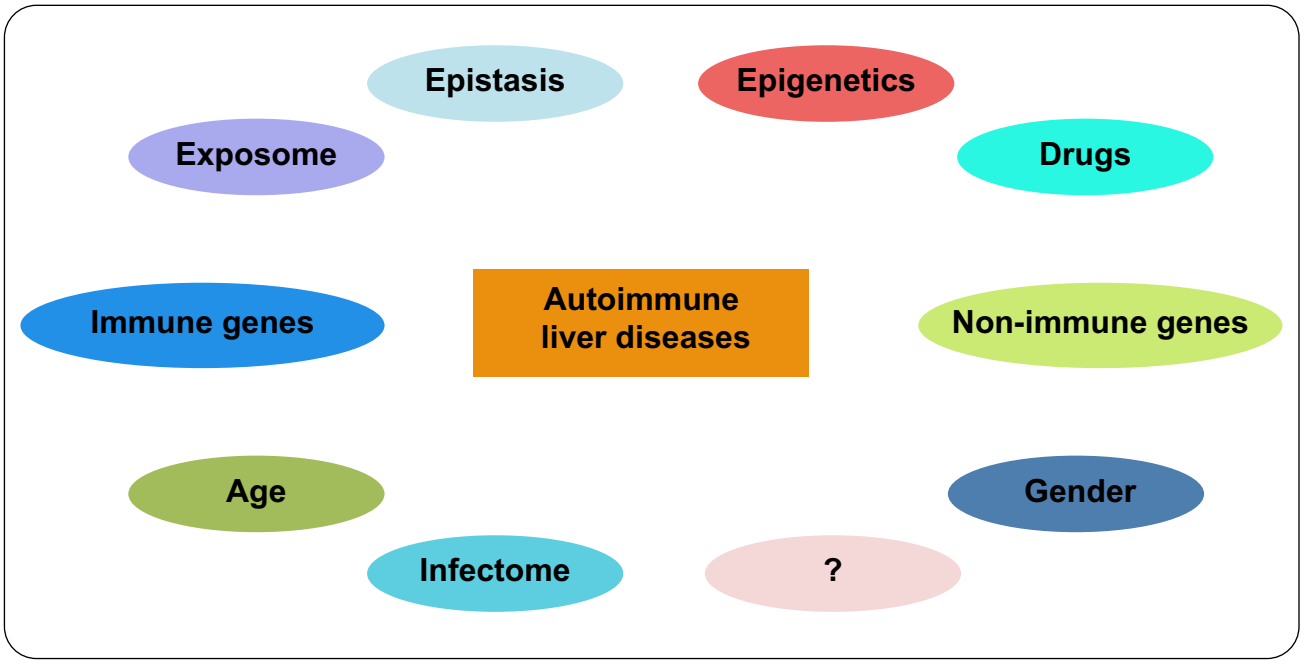

Fig. 1. AIH, PBC, and PSC are complex disorders meaning they are likely associated with the effects of multiple genes in combination with environmental factors.

and progression of fibrosis; those who do not respond to UDCA have a poor survival (10-year survival is >95% and <80% in responders and non-responders to UDCA, respectively) [11]. Other drugs including methotrexate, colchicine and fibrates, have been tested in combination with UDCA but none has been found to be of benefit [12–18]. A promising agent, under investigation is Obeticholic acid (OCA); this is a novel bile acid, which is an agonist of the Farsenoid X receptor implicated in the metabolism and enterohepatic circulation of bile acids [19].

In PSC, treatment with UDCA improves serum liver tests but does not improve survival; indeed, higher doses (17–23 mg/kg/day) are associated with high rates of serious adverse events [20]. Although some units no longer routinely advise their patients with PSC to take UDCA, recent data from the analysis of the UK-PSC cohort [21] of around 700 patients, have shown a dose dependent effect of UDCA on LT-free survival (*UK-PSC – unpublished data*). Thus, for these autoimmune liver diseases there is a subgroup of patients who are non-responders to current treatments and have a poor prognosis, for whom new therapeutic options are warranted. However, development of novel agents is currently hindered by inadequate understanding of the aetiology and pathogenesis of these autoimmune conditions.

Clinical phenotypes of autoimmune liver disease

Clinical and immunological features suggest that AIH is an archetypal autoimmune condition. It is characterized by a strong female preponderance (F:M ratio 7:1); hypergammaglobulinaemia; seropositivity for autoantibodies and a good clinical, serological and histological response to corticosteroids. Furthermore, in AIH concurrent autoimmune disorders occur in approximately 40% of patients, particularly autoimmune thyroid disorder (AITD). Two types of AIH are recognised: type 1 (AIH-1), characterised by antinuclear antibodies (ANA) and/or anti-smooth muscle antibody (SMA), and type 2 (AIH-2), characterised by anti-liver kidney microsomal type 1 antibody (anti-LKM-1) or for anti-liver cytosol type 1 antibody (anti-LC-1) [22].

PBC also exhibits a number of autoimmune features, including the presence of autoreactive T cell and B cell responses against mitochondrial self-antigens, in particular the E2-domain of pyruvate dehydrogenase complex (PDC-E2); the almost universal presence of auto-antibodies reactive with mitochondrial self-antigens; a strong female predominance (F:M ratio, 10:1) and an association with other autoimmune diseases in the same individual and their close family. A concurrent autoimmune disorder occurs in between 32% and 53% of patients, most notably AITD, systemic lupus erythematosus (SLE) or systemic sclerosis (SSc) [23,24]. Autoimmunity is also common in families of PBC patients, with an estimated 14–20% of first degree relatives of PBC probands having an autoimmune disease other than PBC [25,26]. However, unlike AIH, no immunosuppressive agent to date has been shown to be effective in PBC.

PSC is considered an 'autoimmune disease with atypical features' because it displays several differences when compared with the classical autoimmune diseases: these include male predominance (M:F ratio, 2:1), the absence of disease-specific autoantibodies, and the poor response to immunosuppression. However, features that suggest an immune-mediated origin include the major contribution of risk variants within the human leukocyte antigen (HLA) complex, the presence of non-specific autoantibodies, including atypical anti-neutrophil cytoplasmic antibodies (ANCA) [27], the preferential usage of specific T cell receptor variable chains implying the presence of a specific (self)-antigen [28], and a strong association with other autoimmune or immune-mediated disorders which occur in approximately 70% of patients. Most notable is a form of inflammatory bowel disease (IBD), sometimes termed IBD-PSC, which affects up to 90% of patients [29,30]. IBD without any sign of PSC occurs more frequently among first degree relatives of patients with PSC.